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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,128	09/14/2000	Shuji Miyagawa	197330US0	9580

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	20

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/662,128	MIYAGAWA ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5,7-24 and 36* is/are pending in the application.

4a) Of the above claim(s) *12-24 and 36* is/are withdrawn from consideration.

5)☒ Claim(s) *2,3,5,7 and 11* is/are allowed.

6)☒ Claim(s) *8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 2, 3, 5, 7-24 and 36 are pending in the application.

Claims 12-24 and 36 are withdrawn from consideration for being directed to non-elected claims. Claims 6 and 25-35 are cancelled. Claims 2, 3, 5, and 7-11 are currently under examination.

This Office Action is in response to the Amendment filed on 4/29/03.

Response to Amendment

The rejection of claims 5-11 under 35 U.S.C.112 2nd paragraph has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 2, 3 and 7-11 under 35 U.S.C.103 (a) has been withdrawn in light of Applicants' amendment of the claims.

Claims 8-10 are rejected under 35 U.S.C.112 1st paragraph for reasons discussed below.

Election/Restrictions

Applicants request the rejoinder of claims 12-24 with the invention of Group I because Applicants consider the invention of Group I is in condition for allowance. Therefore, Applicants assert that the rejoinder is supported by the practice according to MPEP 821.04.

Applicants' request has been fully considered but deemed unpersuasive. Claims 12-21 are directed to 4 patentably distinct inventions (Groups II and V) for reasons set forth of the record mailed on 2/6/02. The newly added claims 22 and 36 belong to the invention of Group II, and claims 23 and 24 are drawn to method of treating disease which is patentably distinct from the inventions of Group I-V. According to MPEP 821.04, if applicant elects claims directed to

the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined. In the instant case, the inventions of Group I is not directed to a single product but a mixture of products including nucleic acid, vector, organ, tissue, cell and non-human animal. Consequently, MPEP 821.04 does not apply in the current situation. Accordingly, claims 12-24 and 36 are withdrawn from consideration for being directed to non-elected subject matter. Claims 2, 3 and 7-11 are currently under examination.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount

of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

The nature of the invention:

The claims are drawn to a non-human animal, an organ, or a tissue into which the gene encoding a modified Cre recombinase comprising SEQ ID NO:1 is introduced.

The breadth of the claim and teaching of the specification:

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. The breadth of the claim encompasses any tissue, organ or animal that comprise the modified Cre recombinase gene. However, the specification does not teach how to use the tissue that comprises the modified recombinase. The only disclosed use for the organ comprising the modified Cre recombinase is to knockout a xenograft antigen in said organ so that it can be used in organ transplantation. The specification also fails to teach how to use an animal comprising the modified Cre recombinase except a transgenic animal. Moreover, the specification fails to teach how to make transgenic animals comprising Cre recombinase with desired phenotype. Therefore, one skilled in the art would rely on the teaching of the art to determine how to make and use the claimed invention.

The state of art and the level of predictability in the art:

As the current state of the transgenic animal research stands, there are several significant limitations to the generation of transgenic animals with desired phenotype. The mere capability

to perform gene transfer in a given species is not enabling for the claimed transgenic animal because desired phenotype cannot be predictably achieved simply because the animal having the desired genotype. While gene transfer techniques are well developed for a number of species, especially mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection of retrovirus-mediated gene transfer. However, the state of art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p.61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic mouse. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic mouse depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, constructs that use heterologous genetic elements will not always confer the desired phenotype in a mouse. This is especially relevant for the use of genetic elements from species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic mice. Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). Thus, in the absence of specific guidance, the production of a transgene-dependent

phenotypic alteration resulting from introducing a modified Cre recombinase into an animal is unpredictable.

Although there has been some success in the art of xenotransplantation, technical difficulties such as donor choice and immuno-rejection still remains as limiting factors that influences the success of such procedure (see Rowe, 1996, Molecular Medicine Today, pages 10-15). Strategies such as knocking out xenoantigens in donor organ are proposed to decreased the chance of immuno-rejection after transplantation (see Figure 1). However, generation of targeted gene knockout animal such as pig is technically difficult because no ES cells other than mouse has been isolated at present (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p.65). Likewise, Mullins et al. (1996, Clin. Invest. Vol 97, no. 7, 1557-1560) teach that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p.1558, column 2, paragraph 1). Therefore, no knockout animals can be made for any species other than the mouse at the time of filing. However, the organ of mouse is not suitable for transplantation to human. As such, the embodiment of using the organ comprising the Cre recombinase for xenotransplantation is not enabled by the instant specification because the specification fails to teach how to overcome the technical difficulties in discussed in the art.

In view of the art discussed above, whether any transgenic non-human animal comprising modified Cre recombinase gene with desired level of expression can be generated is unpredictable. In addition, whether organ comprising Cre recombinase can be used in xenotransplantation is unpredictable. Without teaching from the specification, one skilled in the art would have to engage in undue experimentation to make and use the invention as claimed.

Conclusion

Claims 2, 3, 5, 7 and 11 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

Celine Qian, Ph.D.
July 10, 2003